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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/392,822	YU ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,14-16,21,24-26 and 32-46* is/are pending in the application.

4a) Of the above claim(s) *47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,14-16,21,24-26 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed September 9, 2000, claims benefit to provision application filed September 10, 1999.

Applicants' amendment filed August 27, 2002, paper number 26, has been received and entered. The specification has been amended. Claims 14-16, 21, 40 and 41 have been amended. Claims 47-54 have been added. Claims 1, 8, 14-16, 21, 24-26 and 32-54 are pending .

Election/Restriction

Newly submitted claims 47-54 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: While newly added claims recite the same preamble at previously presented claims, the new claims set forth a vector that is different and distinct from that previously claimed and examined. Newly added claims set forth a vector requiring two responsive elements controlling the expression two different transgenes. In this case the vectors are structurally different at the specific sequence level and functionally different dependent on the properties of a varying number and use of different promoters.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 47-54 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 1, 8, 14-16, 21, 24-26 and 32-46 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 14-16, 21, 24-26 and 32-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention . Specifically:

The amendment to claims 1 and 35 are unclear and indefinite in the recitation of "in a target cell wherein..." and "in a target cell wherein..." because the claim is drawn to a vector and encompasses specific sequences , and it is unclear how one would know what these particular sequences are given the use of a cell and such functional language that would have to be tested in a particular cell type. Moreover, while the factors or proteins may be present or absent in a particular cell type, it is unclear to what level they must be present to provide the particular effect. For example, if two different cells were demonstrated to express hypoxia inducible factor-1 but at different levels, and one cell underwent cytolysis and the other did not it would be unclear to whether the vector met the limitation of the claims. The claims are indefinite because the functional limitation would be dependent on the cell that is used to test the functional limitation of the vector sequence. Dependent claims are included in the basis of the rejection because they fail to further clarify the basis of the rejection. It is noted that dependent claims recite specific sequences, however the functionality of the vector would also be dependent on the type of cells in which the sequences were present.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 14-16, 21, 25, 26 and 32-46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Henderson *et al.* (WO 97/01358) Hallenbeck *et al.* (WO 96/17053), Walther *et al.* (Mol. Biotechnol., 6:267-286), Dachs *et al.* (Nat. Med., 3(5):515-520,), Dachs *et al.* (Oncol. Res., 9:313-325), Advani *et al.* (Semin. Oncol., 24(6):633-638), and Parr *et al.* (Nat. Med., 3(10):1145-1149).

Applicants note the amendments to the claims and that the regulatory sequences required are activated in a 'cell status' dependent manner. Summarizing the teachings of the cited references, Applicants argue that Walther *et al.*, Dachs *et al.*, Dachs *et al.*, Advani *et al.* do not remedy the deficiency of Henderson *et al.* and Hallenbeck *et al.* to teach replication competent adenoviral vectors with selective cytotoxicity. See Applicants' amendment, bottom of page 8. Applicants' arguments have been fully considered and found persuasive.

As set forth previously, Henderson *et al.* does disclose conditionally replicative-competent adenoviruses designed to limit cytolytic replication to specific cell types due to operable linkage of a cell type-specific TRE to adenoviral genes essential for replication, and optionally carrying a heterologous gene product (see abstract and page 52, claim 21). Further, Henderson *et al.* discloses a preferred embodiment comprising replication competent adenovirus comprising a prostate specific antigen (PSA) TRE comprising a cell status specific enhancer

(nucleotides from 503 to 2086 of SEQ ID NO:3) and a cell status specific promoter (nucleotides from about 5285 to about 5836 of SEQ ID NO:3) operably linked to the adenovirus E1A promoter (i.e. CN706, p. 33-38; as evidenced by p. 49, lines 16-19 of the specification). Hallenbeck *et al.* discloses conditional replication competent adenoviruses to limit cytolytic replication to specific cell types due to operable linking an adenoviral early gene to any one of a number of different tissue or tumor-specific promoters (see abstract and claims 1 and 3). Hallenbeck *et al.* further teaches that the adenovirus vectors of the claimed invention can further comprise a heterologous gene product, such as one that is toxic for cells in the targeted tissue for use in a method of killing cells (page 23, lines 1-4 and claim 8). Clearly Henderson *et al.* and Hallenbeck *et al.* provide the teaching of a replication competent adenoviral vector for the selective killing of a cell. Moreover, the selective killing is affected by the use of the same promoters set forth and encompassed by the instant claims.

With respect to the remaining references, Walther *et al.* reviews the state of the art concerning targeted vectors for gene therapy of cancer and discloses several types of cell status-specific TREs including those comprising a hypoxia responsive elements and heat-inducible elements (see e.g. "Tumor Therapy-Inducible Gene Therapy" section pages 279-281). Walther *et al.* teaches specific radiation-inducible and heat-inducible promoters comprising cell status-specific TREs which "serve as a source for suitable promoters to be exploited for expression regulation of therapeutic genes" (page 279), since radiotherapy and hypothermia, two well-established therapies of human cancers, induce a broad class of cell status-specific promoters that "provide a great potential for the construction of "therapy-inducible" vectors to express auxiliary therapeutic genes that might *act synergistically* with conventional therapies of human tumors"

(emphasis added, from page 281). Walther *et al.* does not explicitly recite the term "cell status-specific TRE" nor does Walther *et al.* refer to hypoxia-inducible response (HRE) elements or cell cycle-specific elements. Dachs *et al.* (Nature Med.) disclose an experimental approach for targeting tumors wherein the hypoxic environment of a tumor can be exploited for activating heterologous gene expression driven by the hypoxia-response element (HRE) comprising a cell status-specific TRE contained in the mouse PGK-1 promoter. Dachs *et al.* teaches that use of HREs can be used to develop gene therapy against the drug- and radiation-resistant hypoxic population in tumors. Dachs *et al.* (Oncol. Res.) reviews the state of the art concerning targeted vectors for gene therapy of cancer and provides a detailed account essentially supporting the use of cell status-specific TREs (page 314). More specifically, Dachs *et al.* discloses several types of cell status-specific- and cell type-specific TREs including those comprising hypoxia responsive- and radiation-responsive TRE elements (in "Condition-Targeted Expression" section, page 318-319). Dachs *et al.* teaches that "severe hypoxia is also a physiological condition specific to tumors, which makes it a potentially exploitable target...[such that they]...have utilized hypoxia response elements (HRE) derived from the oxygen-regulated phosphoglycerate kinase gene to control gene expression in human tumor cells in vitro and in experimental tumors" (abstract, page 313) and that the abnormal hypoxic conditions characterizing almost all solid tumors is "a major hindrance to therapy", since "cells in this aberrant environment can remain viable and are often chemo- and radioresistant" (page 318). Dachs *et al.* further reviews several studies targeting transgene expression to tumorous or ischemic tissues, wherein transgene expression is selectively induced on account of their operable linkage to HRE elements responsive to the hypoxic environment of the diseased tissues. Additionally, Dachs *et al.*

describes the benefits of adenoviral delivery of a Egr-1-controlled TNF-α construct in conjunction with radiation which was shown to result in extensive intratumoral vascular thrombosis and necrosis, whereas no thrombosis was detected in treated normal tissue. Advani *et al.* discloses the benefits of employing cell status-specific TREs comprised of radiation-inducible promoters and teaches that "[i]ncreasing local tumor control by combining radiotherapy and gene therapy may improve the outcome of cancer treatments by decreasing tumor mass more effectively while limiting systemic toxicity. Parr *et al.* discloses adenoviral vectors comprising transgenes operably linked to a E2F-1 promoter containing a cell status-specific TRE that can mediate tumor-selective gene expression in vivo, allowing for eradication of established gliomas with significantly less normal tissue toxicity than seen with standard adenoviral vectors (abstract). Parr *et al.* further point out that since many tumors contain mutations that affect the Rb/E2F pathway, and since de-repression of the E2F-1 promoter occurs in cancer cells in vivo, viral vectors incorporating E2F-responsive promoters can be exploited to design viral vectors that mediate tumor-selective gene expression" (abstract and page 1147, right column).

Thus in summary, Henderson and Hallenbeck teach adenovirus vectors which comprise cell specific TREs. Specific TRE sequences are disclosed and used by Henderson and Hallenbeck, and shown to be effective in the particular cell types tested, however they do not provide other specific TRE sequences or methods and context of use for other cells and conditions. At the time the invention was made it would have been *prima facie* obvious to one of ordinary skill in the art to substitute or combine methods the cell type specific TREs in the conditionally replication-competent adenovirus vectors of Henderson and Hallenbeck with the

cell status-specific TREs disclosed by Walther, Dachs, Advani, or Parr, since each Walther, Dachs, and Advani teach the benefits of combining tumor specific, cell type specific, and/or cell status-specific regulatory elements. One would have been motivated to substitute other specific promoters since the art teaches and supports the use of cell status specific regulatory elements are inducible by well-established treatments, e.g. radiation and hypothermia. Further, Walther, Dachs, and Parr teach that operably linking radiation-inducible, heat-inducible, hypoxia-inducible or cell cycle-inducible regulatory elements (comprising cell status-specific TREs) allows for more effective and selective transgene expression and tumor eradication with significantly less normal tissue toxicity than seen with standard adenoviral vectors. Additionally, substituting and/or combining the cell type-specific regulatory elements of Hallenbeck and Gregory with the cell status-specific TREs of Walther, Dachs, Advani, or Parr would have been in accordance with the goals and teachings of Hallenbeck and Gregory. There would have been a reasonable expectation of success to simply substitute the various promoters taught by Walther, Dachs, Advani, or Parr into the adenovirus constructs of Henderson and Hallenbeck in view of the working examples provided in each of the references which teach the use of the embodiments can be predicted with a high expectation of success.

As summarized in the previous office action, Henderson and Hallenbeck each teach adenovirus vectors which comprise cell specific TREs and propose the use of these vectors to affect various treatments. Walther, Dachs, Advani, and Parr are relied upon for the teaching of specific promoters and each teach and provide the motivation of the benefits of combining tumor specific, cell type specific, and/or cell status-specific regulatory elements in the context of various vectors. Thus, it is maintained that at the time the invention was made it would have

been *prima facie* obvious to one of ordinary skill in the art to substitute or combine methods the cell type specific TREs in the conditionally replication-competent adenovirus vectors of Henderson and Hallenbeck with the cell status-specific TREs disclosed by Walther, Dachs, Advani, or Parr, since each Walther, Dachs, and Advani teach the benefits of combining tumor specific, cell type specific, and/or cell status-specific regulatory elements. Additionally, one would have been motivated to substitute other specific promoters since the art teaches and supports the use of cell status specific regulatory elements are inducible by well-established treatments, e.g. radiation and hypothermia, and that operably linkage to radiation-inducible, heat-inducible, hypoxia-inducible or cell cycle-inducible regulatory elements (comprising cell status-specific TREs) allows for more effective and selective transgene expression and tumor eradication with significantly less normal tissue toxicity than seen with standard adenoviral vectors.

It is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). In the instant case, given the level of skill in the art for generating polynucleotide vectors, there is a reasonable expectation that the artisan can combine the various vector elements to produce the vectors encompassed by the instant claims.

Thus, for the reasons above and of record, the invention was *prima facie* obvious at the time the invention was made, and therefore, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach